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TRAJECTORIES OF DEPRESSIVE EPISODES AND HYPERTENSION OVER 24 YEARS: THE WHITEHALL II PROSPECTIVE COHORT STUDY

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Abstract

Prospective data on depressive symptoms and blood pressure (BP) are scarce, and the impact of age on this association is poorly understood. The present study examines longitudinal trajectories of depressive episodes and the probability of hypertension associated with these trajectories over time. Participants were 6,889 men and 3,413 women London based civil servants, aged 35-55 years at baseline, followed for 24 years between 1985 and 2009. Depressive episode (defined as scoring 4 or more on the General Health Questionnaire-Depression subscale or using prescribed antidepressant medication) and hypertension (systolic/diastolic blood pressure ≥ 140/90 mm Hg or use of antihypertensive medication) were assessed concurrently at five medical examinations. In the fully adjusted longitudinal logistic regression analyses based on Generalized-Estimating-Equations using age as the time scale, participants in the "*increasing depression*" group had a 24% ($p<0.05$) lower risk of hypertension at ages 35-39, compared to those in the "*low/transient depression*" group. However, there was a faster age-related increase in hypertension in the "*increasing depression*" group, corresponding to a 7% ($p<0.01$) greater increase in the odds of hypertension for every each five-year increase in age. A higher risk of hypertension in the first group of participants was not evident before age 55. A similar pattern of association was observed in men and women although it was stronger in men. This study suggests that the risk of hypertension increases with repeated experience of depressive episodes over time and becomes evident in later adulthood.

Key words: Depression, hypertension, longitudinal analysis, repeated measures

INTRODUCTION

The impact of depression on the development and prognosis of chronic diseases such as coronary heart disease (CHD) has attracted significant research attention in recent years. In healthy populations, long-term prospective studies have found depression to be associated with the development of CHD, independently of other coronary risk factors.[1-3] Successive meta-analyses [1, 4, 5] show a pooled relative risk between 1.6 and 1.8 for incident CHD in subjects with depressive symptoms or diagnosed depression. However, the mechanisms underlying the association between depressive disorders and CHD remain unclear.

Hypertension or high blood pressure (BP) often accompanies psychological stress [6] and has therefore been posited as a candidate mechanism for the depression-CHD link [7]. Several studies have examined the association between depressive disorder (or symptoms) and blood pressure, but the findings are mixed. While some studies found an association between increased BP / hypertension and depression symptoms,[8-11] others reported no such association[12, 13] or found an inverse association such that lower blood pressure was observed in depressed patients [9, 14-18]. However, most of these studies have important limitations, such as a cross-sectional design [9, 15, 16, 18-20], low statistical power, a restricted age range (elderly populations) [16, 17, 19, 20], or lack of repeated measures for blood pressure or depression[8, 9, 15, 16, 18, 19].

The present study takes advantage of five waves of medical screening data from the British Whitehall II study to examine prospectively the associations between trajectories of depressive episodes assessed at five points in time over a 24-year period with hypertension assessed at five clinical examinations over the same period of follow-up.

MATERIAL & METHODS

Data are drawn from the Whitehall II study, established in 1985 as a longitudinal study to examine the socioeconomic gradient in health and disease among 10,308 civil servants (6,895 men and 3,413 women). All civil servants aged 35-55 years in 20 London-based departments were invited to participate by letter and 73% agreed. The first screening (Phase 1) took place during 1985-1988, and involved a clinical examination and a self-administered questionnaire. Subsequent phases of data collection have alternated between postal questionnaire alone [Phases 2 (1989-1990), 4 (1995-1996), 6 (2001) and 8 (2006)) and postal questionnaire accompanied by a clinical examination (Phases 3 (1991-1993), 5 (1997-1999), 7 (2002-2004) and 9 (2007-2009)]. All participants gave consent to participate and the University College London ethics committee approved this study.

Measures

Assessment of depressive episodes at phases 1, 3, 5, 7, 9

The General Health Questionnaire is used to detect minor psychiatric disorders in non-psychiatric populations [21]. Symptoms of depression were measured using a four-item scale (Cronbach α=0.88) derived from the 30-item GHQ, which has been validated within the Whitehall II study [22] based on principal components factor analysis and a comparison with the seven-item severe depression subscale from the 28-item GHQ [23]. At each phase, respondents were considered as having depressive episode if they scored 4 or more on the depression subscale or reported the use of prescribed antidepressant medication [23].

Assessment of hypertension at phases 1, 3, 5, 7, 9

Systolic BP (SBP) and diastolic BP (DBP) were measured twice in the sitting position after 5 minutes of rest with the Hawksley random-zero sphygmomanometer at phases 1, 3, and 5 and OMRON HEM 907 at phases 7 and 9 [24]. For the analyses, hypertension was defined according to the seventh report of the Joint National Committee on Prevention, Detection,

Evaluation, and Treatment of High Blood Pressure (systolic/diastolic >=140/90 mm Hg or use of antihypertensive medication) [25].

Age as time scale

As we wanted to model the age-related probability of hypertension as a function of depressive-episodes-trajectory groups, we used age rather than the phase of data collection as the time scale in the longitudinal analysis (i.e., the age recorded for each participant at the time of each phase)**.** Participants were 35-55 years old at phase 1 (baseline) and 55-80 years old at phase 9. This implies that the participants provided data across the whole age range (35-80) as a function of their age between the baseline and the last follow-up. To allow estimates of the probability of hypertension as a function of age, we created five-year age categories as follows: 35-39, 40-44, 45-49, 50-54, 55-59, 60-64, 65-69, 70-74, 75-80 years.

Covariates

Sociodemographic measures

Sociodemographic measures included sex, ethnicity, marital status and socioeconomic status (SES) assessed by British civil service grade of employment taken from the baseline (phase 1) questionnaire.

Biobehavioural risk factors

Biobehavioural risk factors were assessed using responses to the baseline (phase 1) questionnaire and categorised as follows: smoking status (never, former, and current), physical activity (≥1.5 or <1.5 hours of moderate or vigorous exercise/week), high alcohol consumption in the previous week (14+ units for women/21+ units for men). Biological risk factors were assessed at phase 1 clinical examination and included body mass index (BMI) (<20, 20-24.9, 25-29.9, or ≥30 kg/m^2), high total blood cholesterol (≥ 5 mmol/l). History of chronic medical conditions including diabetes, myocardial infarction, stroke and cancer were assessed at phase 1 questionnaire via self-reports of doctor diagnosis.

Statistical analysis

The statistical analysis included the following steps. First, we modelled trajectories of depressive episodes by using the SAS procedure PROC TRAJ [26] that separates individuals into trajectory groups, here based on the depressive episode status (yes/no) of each participant at each of five assessment points (phases) over the 24-year follow-up period. We identified two distinct trajectories of depressive episodes: the first trajectory composed of 88.7% of the study sample and was characterized by participants with no or few depressive episodes during the entire study period, the *"low/transient depression" group*. In this group, the prevalence of depressive episodes at the 5 successive follow-ups was: 9.0%, 7.9%, 5.5%, 4.0% and 3.0%. The second trajectory, labelled the *"increasing depression"* group, was composed of 11.3% of the study population and included participants with an increase in the number of depressive episodes over time; 50.4%, 40.3%, 65.8%, 74.6% and 66.0% at the five follow-ups, respectively. Details on the construction of these two trajectory groups are available elsewhere (please see http://hyper.ahajournals.org, *appendix 1*).

Second, we examined differences in the two trajectory groups (defined by depressive episodes) as a function of baseline sociodemographic and biobehavioral covariates using the chi-square statistic and a one way analysis of variance.

Third, we examined associations between covariates and hypertension status at baseline and over the follow-up period by fitting longitudinal logistic regression models implemented with generalized estimating equations (GEEs)[27]. In these models, the dependent variables were the five repeated measures of hypertension over the 24-year period of follow-up. Separate models were fitted that estimated an effect of age, modelled as a 5-year increase in age, and sex together with their interaction. Subsequent models additionally included: 1) the sociodemographic and biobehavioral covariates, and 2) the interactions between each covariate and age. Only associations with a $p<0.05$ were retained as covariates in subsequent analyses.

Fourth, to examine the association between trajectory groups (defined by depressive episodes) and hypertension over the follow-up period, we fitted four sequential longitudinal logistic regression models using GEEs. In model 1, age, trajectory groups, interaction term between trajectory groups and age were the predictor variables, adjusting for sex, interaction between sex and age, ethnicity and socioeconomic status. Models 2 and 3 are as model 1 but additionally adjusted for biobehavioural risk factors and their interactions with age (when significant at $p<0.05$), and for chronic medical conditions and their interactions with age when significant at $p<0.05$, respectively. Model 4 simultaneously adjusted for all aforementioned variables and their interactions with age. The results of the GEE-analyses are presented as odds ratios (ORs) with 95% confidence intervals (CI). We show results from analyses stratified by, and adjusted for, sex. Finally, we illustrated graphically the relationship between depressive episodes trajectories and the risk of hypertension over time using predicted probabilities from the GEE-analyses at ages 35-39, 40-44, 45-49, 50-54, 55-59, 60-64, 65-69, 70-74, 75- 80 in men and women.

RESULTS

Prevalence of depressive episodes and hypertension across phases

The prevalence of depressive episodes remained largely unchanged across the study phases (not shown in the tables): 13.9% at phase 1 (baseline), 11.6% at phase 3, 13.9% at phase 5, 14.1% at phase 7 and 12.1% at phase 9 (p=0.372). In contrast, there was a clear increase in the prevalence of hypertension over the course of the study: 19.3% at Phase 1, 17.9% at phase 3, 27.1% at phase 5, 39.5% at phase 7, and 46.8% at phase 9 (p<0.001)(not shown in the tables).

Trajectory groups (defined by depressive episodes) and baseline characteristics

Table 1 presents the baseline characteristics of the two trajectory groups. Compared to the "*low/transient depression*" group, participants in the "*increasing depression"* group had lower BMI, were younger, less physically active, more likely to be female, more likely not to be married/cohabiting, high alcohol consumers, and from the lower SES group (all $p\leq0.022$).

Baseline covariates and risk of hypertension over time

Table S1 shows the associations between baseline covariates, their interaction with time (here age) and hypertension over time (please see http://hyper.ahajournals.org, *Table S1*). The odds ratio (OR) for age was 1.36 ($p<0.001$) indicating that the odds for hypertension increased by 36% for every five-year increase in age over the follow-up. At ages 35-39, women had lower odds for hypertension than men ($p<0.001$) but it increased more rapidly with age in women than in men (an excess increase of 9% for every five-year increase in age, $p<0.001$). Non-white ($p<0.01$), non-married/cohabiting ($p<0.001$) and low SES participants ($p<0.001$) had higher odds for hypertension at ages 35-39, but for the latter two covariates, the increased odds for hypertension overtime decreased by 5% and 4% respectively for every five-year increase in age. Current smokers had lower odds of hypertension at ages 35-39 ($p<0.01$), but they experienced greater increase over time compared to those who had never smoked (an excess increase of 6% for every five-year increase in age, $p<0.01$). Participants above the lowest weight category had higher odds ratios for hypertension ($p\leq 0.001$) and there was a suggestion that these increased with age. Participants with high total blood cholesterol level had higher odds for hypertension ($p< 0.001$) and this did not differ by age. Participants with a history of cancer at ages 35-39 have a much reduced odds of hypertension ($p<0.01$) it increased by 17% for every 5 years increase in age ($p<0.05$).

Trajectory groups (defined by depressive episodes) and risk of hypertension over time

Table 2 presents the risk of hypertension over time in the "*increasing depression*" group compared to that in the "*low/transient depression*" group. This analysis is based on 40 599 observations over the follow-up among 10302 participants (6389 men and 3413 women). After adjustments for sex, interaction between sex and age, ethnicity, marital status, interaction between marital status and age, SES and interaction between SES and age (model 1), participants in the "*increasing depression*" group had reduced odds for hypertension at ages 35-39 (OR=0.75, 95% CI, 0.61-0.92). However, the statistically significant interaction term with

age suggests that this group experienced greater increase in the risk for hypertension with advancing age; an excess increase of 7% (95% CI, 3-12) in the odds for hypertension for every five-year increase in age. Further adjustments for physical activity, smoking, interaction between smoking and age, BMI, and total cholesterol (model 2), diabetes, history of myocardial infarction, history of stroke, history of cancer, interaction between history of cancer and age (model 3) and for all aforementioned variables and interactions (model 4) did not alter these associations. The pattern of results was similar in men and women although the associations were somewhat stronger in men than in women.

Figures S2 (men) and *S3* (women) [please see http://hyper.ahajournals.org, *Figures S2 and S3]* show that the probability of hypertension in the low/transient and increasing depressive episode groups increased with increasing age, but with the size of the increase differing between the groups. Thus, the probability for hypertension between the ages of 35 and 55 years was slightly lower among participants in the "*increasing depression*" group, both in men and women, compared to those in the "*low/transient depression*" group. However, at ages 50-54 the prevalence of hypertension increased more rapidly among men in the "*increasing depression*" group, leading to higher probability of hypertension at the end of the follow-up in this group. In women, this seems to occur much later.

Sensitivity analysis

In order to test the robustness of our findings, we undertook several sensitivity analyses. First, we excluded the use of antidepressant and antihypertensive medications from the definition of depressive episode (a score ≥ 4 on the depressive symptoms scale) and hypertension (systolic/diastolic blood pressure ≥ 140/90 mm Hg) respectively. In analysis adjusted for covariates, as in Model 4 of the main analyses, we found a similar pattern of associations to that reported in the main analysis. Participants in the "*increasing depression*" group had reduced odds of hypertension at ages 35-39 (OR=0.69, $p<0.01$) compared to those in the *"low/transient depression"* group. However, this group experienced a greater increase in the

risk for hypertension with advancing age; an excess increase of 7% ($p<0.01$) for every five-year increase in age.

Secondly, we excluded participants using antidepressant and antihypertensive medications from the analyses (n observations = 28024) and found the associations to be close to those reported in the main analysis and the first sensitivity analysis. Here again, participants in the "*increasing depression*" group had reduced odds for hypertension at ages 35-39, (OR=0.69, $p<0.05$) compared to those in the *"low/transient depression"* group. However, this group experienced a greater increase in the risk for hypertension with advancing age; an excess increase of 8% ($p<0.05$) for every five-year increase in age. These findings suggest that the associations observed in the main analysis are unlikely to be driven by antidepressant and/or antihypertensive medications.

Thirdly, we undertook further analysis using an alternative definition of depressive episodes trajectories. This was based on the number of depressive episodes over the five assessments, calculated for each participant. Longitudinal logistic regression analyses with GEE revealed that participants with 3-5 depressive episodes had a slightly lower odds of hypertension at ages 35-39 (0.70, 95% CI 0.53-0.94) compared to those with no depressive episodes, but a steeper increase in risk with advancing age (excess odds 9%, 95% CI 3-15 for each five-year increase in age). No difference in the risk of hypertension was observed between participants with 1-2 depressive episodes and those with no such episodes. These results are highly consistent with those reported in the main analyses using trajectories of depressive episodes, demonstrating the importance of recurrent or chronic depressive symptoms for hypertension risk

DISCUSSION

In this study, we sought to examine longitudinal associations between trajectories of depressive episodes and risk of hypertension, both assessed five times over a 24-year follow-up period. In the longitudinal analysis, adjusted for sociodemographic characteristics, participants in the "*increasing depression*" group had a 25% lower risk of hypertension at ages 35-39 when compared to those in the "*low/transient depression*" group. However, there was a faster age-related increase in hypertension in the "*increasing depression*" group, corresponding to a 7% greater increase in the odds of hypertension for every five-year increase in age. Thus, the risk of hypertension in participants in the "*increasing depression*" group at the end of the follow-up was substantially higher than that in the "*low/transient"* group. This pattern of association was observed in both men and women even though the associations were stronger in men.

Findings in context of the literature

Several studies that have examined the association of depressive disorders (and symptoms) with blood pressure have produced mixed findings [8-10, 12-20] . Our data suggest that cross-sectional assessment of both depressive symptoms and hypertension may partly account for these inconsistencies in the existing literature. As far as we are aware, our study is the first to examine the associations between longitudinal patterns of depressive episodes and risk of hypertension in a large population of adults where both measures were assessed repeatedly over time. As depressive episodes tend to fluctuate over time and there is a general age-related increase in blood pressure levels, with substantial inter-individuals variation [28, 29] , it is crucial to use longitudinal data to examine the dynamics between depressive symptoms and hypertension. Using a longitudinal modelling approach we were able to accounting for the effect of advancing age on the risk of hypertension., extending previous research where depressive symptoms at baseline were used to predict incident hypertension during the follow-up[12, 13, 30].

Overall, in our study, the risk of hypertension associated with age increased more rapidly among participants who experienced more depressive episodes than among those with low

levels of depressive episodes. This is in line with the idea that continuing psychological distress has clinically relevant physiological effects [30,31]. Nevertheless, our finding of a low risk of hypertension before the age of 55 (in men) which increases thereafter is in contrast with other studies. A large cross-sectional study including individuals aged 20 to 89 years found no age differences in the inverse association between depression and BP[15] . In addition, a recent prospective study found that depression was associated with increased risk of hypertension in middle-aged but not in elderly individuals[11].

Our longitudinal analysis showing a greater increase in the risk of hypertension among individuals with high depression levels over time lends support to the hypothesis that depressive disorder (or symptoms) may increase BP levels and lead to hypertension[8-10]. Several plausible mechanisms may explain this association. First, as hypertension develops over a long time span, it may be that depressive symptoms in the long- rather than the short-term influence risk of high BP or hypertension. Thus, the trend toward an increase in the odds for hypertension in participants in the *"increasing depression"* group could be seen as a consequence of depressive symptoms that are likely to be persistent, severe or less responsive-to-treatment. This could also explain why we observed that the risk of hypertension among men in the "*increasing depression*" group started to strengthen after the age of 55 years. Second, it has been proposed that depressive symptoms could be linked to hypertension through their effect on the autonomic nervous system involved in the regulation of blood pressure[32]. The effect of depressive symptoms on autonomic dysfunction could also be due to their association with other mental disorders, panic disorder in particular, rather than a direct effect [33]**.** Third, depressive symptoms are associated with various health-related behaviours that could then impact the risk of hypertension. However, adjustment for smoking status, physical activity, alcohol intake and BMI at baseline did not alter the results in our study. Fourth, the observed association could be due to a common cause or a confounder. For instance, with aging there is a rapid increase in the risk of a number of medical conditions, such as cancer, diabetes, heart disease, and arthritis,

which are known to be associated with depression [34, 35]. It is possible that the age-related increase in chronic medical conditions among older individuals affects both the occurrence of depressive episode and hypertension, leading them to be associated when there is no causal association between the two. Finally, we cannot completely rule out the possibility of reverse causation since hypertension awareness may induce psychological distress [36]. Further research is needed to clarify the precise mechanisms through which long-term patterns of depressive episodes are related to high blood pressure and its increase over time. Longitudinal modelling of some of the covariates included in this study may also allow better exploration of the mechanisms underlying the associations we have observed.

Study limitations

In interpreting the present results, it is important to note some limitations. First, this cohort of civil servants did not include blue collar and unemployed workers; thus it is not representative of the general population limiting the generalisability of our findings. Second, our data on depressive symptoms are limited to cognitive manifestations. Given that previous studies have shown clinical depression to be a stronger predictor of coronary heart disease than depressive mood [5], the present study may have underestimated the true association between depression and hypertension.

Despite these potential limitations, the present findings are important as this is the first large-scale study to show the longitudinal patterns in the association of depressive episodes and hypertension, both assessed repeatedly over an extended follow-up period. The study provides robust evidence to suggest that increased depressive episodes over time are associated with a higher risk of hypertension which appears to become apparent in late adulthood (age 55+).

Perspectives

Our findings suggest that cross-sectional associations between depressive episodes and blood pressure in non-elderly populations might be uninformative. There seem to be both age- and time-related patterns of depressive episodes and thus it is reasonable to assume that long-

term patterns of depressive episodes over time may be more pertinent for hypertension than depressive episodes at a single point in time. Epidemiological studies with repeated measures are now widespread and our findings suggest that such data are important to examine the dynamics of the association between depressive symptoms and hypertension.

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Table 1. Baseline characteristics in two depressive episodes trajectory groups

Variables	N total	Depressive episodes trajectory groups		
		Low/transient N (%)	Increasing N (%)	*p-value*
Age , Mean (SD)	10302	44.56 (6.06)	43.55 (5.89)	<0.0001
Sex				0.003
Women	3413	2981 (87.3)	432 (12.7)	
Men	6889	6153 (89.3)	736 (10.7)	
Ethnicity				0.21
White	9177	8149 (88.8)	1028 (11.2)	
Other	1125	985 (87.6)	140 (12.4)	
Marital status				<0.0001
Married/cohabiting	7603	6823 (89.7)	780 (10.3)	
Other	2661	2278 (85.6)	383 (14.4)	
Missing	38	33 (86.8)	5 (13.2)	
Socioeconomic status				0.0005
High	3027	2739 (90.5)	288 (9.5)	
Intermediate	4939	4354 (88.2)	585 (11.8)	
Low	2336	2041 (87.4)	295 (12.6)	
Physical activity				<0.0001
No	3261	2820 (86.5)	441 (13.5)	
Yes	6529	5856 (89.7)	673 (10.3)	
Missing	512	458 (89.5)	54 (10.5)	
Smoking status				0.30
Never	5062	4486 (88.6)	576 (11.4)	
Ex	3269	2921 (89.4)	348 (10.6)	
Current	1882	1649 (87.6)	233 (12.4)	
Missing	89	78 (87.6)	11 (12.4)	
High alcohol intake				0.001
No	8609	7672 (89.1)	937 (10.9)	
Yes	1599	1386 (86.7)	213 (13.3)	
Missing	94	76 (80.9)	18 (19.1)	
BMI				0.022
<19.9	610	519 (85.1)	91 (14.9)	
20-24.9	5642	4996 (88.6)	646 (11.4)	
25-29.9	3314	2969 (89.6)	345 (10.4)	
>30	726	642 (88.4)	84 (11.6)	
Missing	10	8 (80.0)	2 (20.0)	
Cholesterol total >5mg/l				0.34
No	2241	1970 (87.9)	271 (12.1)	
Yes	7989	7102 (88.9)	887 (11.1)	
Missing	72	62 (86.1)	10 (13.9)	
Diabetes				0.915
No	10202	9045 (88.7)	1157 (11.3)	
Yes	100	89 (89.0)	11 (11.0)	
History of myocardial infarction				0.58
No	10267	9104 (88.7)	1163 (11.3)	
Yes	35	30 (85.7)	5 (14.3)	

History of stroke				0.97
No	10275	9110 (88.7)	1165 (11.3)	
Yes	27	24 (88.9)	3 (11.1)	
History of cancer				0.98
No	10188	9033 (88.7)	1155 (11.3)	
Yes	114	101 (88.6)	13 (11.4)	
Antihypertensive medication				0.86
No	9967	8836 (88.7)	1131 (11.3)	
Yes	335	298 (89.0)	37 (11.0)	
Antidepressive medication				<0.0001
No	10180	9073 (89.1)	1107 (10.9)	
Yes	122	61 (50.0)	61 (50.0)	
SBP, Mean (SD)	10290	123.32 (14.79)	121.20 (14.41)	<0.0001
DBS, Mean (SD)	10289	77.03 (10.24)	76.05 (10.14)	0.0022

Note: BMI, body mass index; MI, myocardial infarction; SBP, systolic blood pressure; DBP, diastolic blood pressure

Table 2. Associations between trajectories of depressive episodes and probability of hypertension over time

Variables	Odds ratios (95% CI) for hypertension over time		
	Men & Women N observations = 40599	Men N observations = 27922	Women N observations = 12677
Model 1			
Depressive episodes trajectory groups			
low/transient depression	1	1	1
increasing depression	0.75 (0.61, 0.92) †	0.76 (0.59, 0.97) *	0.69 (0.47, 1.01)
Depressive episodes trajectory groups x age			
low/transient depression	1	1	1
increasing depression	1.07 (1.03,1.12) †	1.10 (1.04, 1.15) ‡	1.04 (0.97, 1.12)
Model 2			
Depressive episodes trajectory groups			
low/transient depression	1	1	1
increasing depression	0.76 (0.62, 0.94) *	0.76 (0.59, 0.98) *	0.71 (0.48, 1.04)
Depressive episodes trajectory groups x age			
low/transient depression	1	1	1
increasing depression	1.07 (1.03, 1.12) †	1.10 (1.04, 1.15) ‡	1.05 (0.97, 1.13)
Model 3			
Depressive episodes trajectory groups			
low/transient depression	1	1	1
increasing depression	0.75 (0.61, 0.92) †	0.76 (0.59, 0.97) *	0.69 (0.47, 1.02)
Depressive episodes trajectory groups x age			
low/transient depression	1	1	1
increasing depression	1.07 (1.03, 1.12) †	1.10 (1.04, 1.15) ‡	1.04 (0.97, 1.12)

Model 4			
Depressive episodes trajectory groups			
low/transient depression	1	1	1
increasing depression	0.76 (0.62, 0.94) *	0.76 (0.59, 0.98) *	0.71 (0.49, 1.04)
Depressive episodes trajectory groups x age			
low/transient depression	1	1	1
increasing depression	1.07 (1.03, 1.12) †	1.09 (1.04, 1.15) ‡	1.04 (0.97, 1.13)

*p <0.05; † p<0.01; ‡ p<0.001
Model 1: OR adjusted for sex, age, sex xage, ethnicity, marital status, marital status * age, socioeconomic status and socioeconomic status and age
Model 2: Model 1 additionally adjusted for physical activity, smoking status, smoking status * age, bmi and cholesterol
Model 3: Model 1 additionally adjusted for diabetes, history of myocardial infarction, history of stroke, history of cancer, history of cancer * age
Model 4: Model 1 additionally adjusted for all aforementioned variables
Note: In each model there are two ORs. The first estimates the association between depressive episodes trajectory groups and probability of hypertension at ages 35-39 (reference). The second estimates the proportional change in this association for every 5-years increase in age.